Recommendations From the 2016 Guidelines for the Management of Adults With Hospital-Acquired or Ventilator-Associated Pneumonia

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INTRODUCTION

Hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) continue to represent the most common nosocomial-associated infections, resulting in significant attributable mortality, increased length of hospital stay, and financial burden.[1] The updated Infectious Diseases Society of America (IDSA) guidelines provide guidance on the diagnosis and management of nonimmunocompromised hosts with HAP and VAP.

HAP is defined as pneumonia that develops at least 48 hours following hospitalization, while VAP is defined as pneumonia that develops at least 48 hours after intubation. It is important to note that the guidelines make a total of 47 recommendations; none are based on "strong quality of evidence," and only seven are based on "moderate-quality evidence." Key changes from the previous guidelines include: 1) removal of the health care-associated pneumonia (HCAP) entity; 2) emphasis on developing local antibiograms to aid health care providers in selecting empiric antibiotics; 3) new indications for empiric dual gram-negative and methicillin-resistant *Staphylococcus aureus* (MRSA) therapy, and 4) a seven-day duration of antibiotic therapy.

RATIONALE FOR REMOVING HCAP FROM GUIDELINES

In the 2005 IDSA guidelines, the HCAP designation was used for patients thought to be at high risk for multidrug-resistant (MDR) organisms due to their contact with the health care system. However, there is increasing evidence that many patients defined as having HCAP are not at high risk for MDR pathogens.[1] In a meta-analysis of 24 studies comparing the frequency of resistant pathogens in populations with HCAP versus community-acquired pneumonia (CAP), HCAP was associated with an increased risk of MRSA, *Enterobactericeae*, and *Pseudomonas aeruginosa* ($P < 0.0001$). The discriminatory ability of HCAP for resistant pathogens was found to be low, and it was lower in high-quality and prospective studies.[2] Later, in a retrospective study among adults hospitalized with community-onset pneumonia, MDR organisms were isolated in 5.9% and 1.9% of HCAP and CAP patients, respectively. The presence of an MDR organism was not found to be associated with HCAP classification or with most of its individual components (hemodialysis, home infusion, home wound care, and hospitalization for at least 48 hours in the last 90 days). Independent predictors of MDR included: *P. aeruginosa* colonization or infection in the previous year ($P < 0.001$), antimicrobial use in the previous 90 days ($P = 0.027$), and admission from a nursing home ($P = 0.005$). While the HCAP definition of hospitalization for more than 48 hours in the previous 90 days was not a predictor of MDR isolation, the total number of days hospitalized in the previous 90 or 180 days was ($P = 0.013$ and $P = 0.002$, respectively).[3] To further support these results, a prospective study compared patients with HCAP, patients with CAP, and immunocompromised patients (ICP) with severe pneumonia admitted to the intensive care unit (ICU). The study included 726 patients with pneumonia (CAP, 449; HCAP, 133; and ICP, 144). HCAP patients had more comorbidities and worse clinical status. HCAP patients and immunocompromised patients needed mechanical ventilation and tracheotomy more frequently than CAP patients. *Streptococcus pneumoniae* was the most frequent pathogen in all three groups (CAP, 34.2%; HCAP, 19.5%; and ICP, 23.4%; $P = 0.001$). The incidence of *P. aeruginosa, Acinetobacter baumannii, Serratia marcescens, Stenotrophomonas maltophilia, Klebsiella pneumoniae*, and MRSA was low, but higher in HCAP patients (9.8%) and immunocompromised patients (7.0%) than in patients with CAP (3.3%) ($P = 0.008$). Empiric treatment was in line with CAP guidelines in 73.5% of patients with CAP, in 45.5% of patients with HCAP, and in 40% of immunocompromised patients, and within the first 24 hours of diagnosis, was 6.5% (CAP), 14.4% (HCAP), and 21.8% (ICP) ($P < 0.001$). Mortality was highest in immunocompromised patients (38.6%) and did not differ significantly between CAP (18.4%) and HCAP (21.2%) patients. This showed that empiric antibiotic therapy recommended for CAP would be appropriate for 90% of patients with HCAP in this population, based on bacterial pathogens identified.[4] As a result of these findings, HCAP was excluded from the 2016 HAP/VAP guidelines. Recommendations for the HCAP population may be addressed in the upcoming CAP guidelines, which are currently undergoing revision.

DIAGNOSIS OF HAP/VAP

The definition of HAP/VAP has not changed from the 2005 guidelines.[5] Pneumonia was defined as the presence of "new lung infiltrate plus clinical evidence that the infiltrate is of an infectious origin, which includes the new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation." Despite these definitions, it is often difficult to distinguish between pneumonia and other noninfectious etiologies, such as congestive heart failure, that also have imaging with non-

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Table 1 Risk Factors for Infection by Multidrug-Resistant Organisms

Type of Pathogen	Risk Factors	
	Hospital-Acquired Pneumonia	Ventilator-Associated Pneumonia
MDR organisms	• Prior IV antibiotic use within 90 days	• Prior IV antibiotic use within 90 days • Septic shock at time of VAP • Acute respiratory distress syndrome preceding VAP • Five days of hospitalization before VAP onset • Acute renal replacement therapy prior to VAP onset
Methicillin-resistant *Staphylococcus aureus*	• Prior IV antibiotic use within 90 days • Need for ventilatory support for septic shock	• Prior IV antibiotic use within 90 days
MDR *Pseudomonas*	• Prior IV antibiotic use within 90 days • Need for ventilatory support for septic shock	• Prior IV antibiotic use within 90 days

HAP = hospital-acquired pneumonia; IV = intravenous; MDR = multidrug resistant; VAP = ventilator-associated pneumonia.

specific lung changes or in which infiltrates cannot be ruled out. In addition, because cultures taken from an endotracheal tube will likely be positive due to pooling of secretions and the development of a biofilm, distinguishing colonization from clinically significant pathogens represents another challenge.[6,7] This may complicate the clinical picture, and patients are often overdiagnosed and consequently treated for "pneumonia." Although the authors of the current guidelines note that "there is no gold standard for the diagnosis of HAP or VAP," obtaining cultures is recommended in the evaluation of these patients.

For the diagnosis of VAP, the guidelines recommend non-invasive (endotracheal aspiration) sampling with semiquantitative cultures. If invasive sampling is performed for suspected VAP and the culture results do not confirm the diagnosis, the guidelines suggest withholding antibiotics.[1] This may be of benefit because it decreases antibiotic use, which in turn decreases the number of complications from antibiotic therapy and the potential for the development of MDR pathogens.[1]

For the diagnosis of HAP, the guidelines suggest that definitive treatment should be based upon respiratory culture results rather than empiric therapy. Although there is a lack of evidence demonstrating improved clinical outcomes with respiratory cultures in suspected HAP patients, obtaining cultures will allow antibiotic therapy to be tailored to the recovered organisms. This may broaden initial empiric antibiotic treatment if recovered pathogens are MDR or allow for de-escalation to agents with a narrower spectrum.

EMPIRIC TREATMENT

The current guidelines highlight the importance of using routinely updated institutional antibiograms to determine the best empiric antimicrobial regimens based on local distribution of pathogens and their antimicrobial susceptibilities. The goal is to choose antibiotics that target specific pathogens associated with HAP/VAP as narrowly as possible; this will ensure optimal treatment while minimizing overtreatment and negative outcomes. In addition to local antibiograms, patient-specific risk factors (Table 1) should be used to identify patients at risk for MDR organisms who may necessitate coverage of MRSA or double coverage for *Pseudmonas* until susceptibilities are available.

In patients with HAP/VAP without risk factors for MDR organisms (Table 1), empiric therapy should include one antibiotic with activity against *P. aeruginosa*, other gram-negative organisms, and methicillin-sensitive *S. aureus*. Suggested agents include piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem, with a caveat that agent selection be based on local antibiograms. Notably, monotherapy with antipseudomonal activity suffices as long as local resistance does not exceed 10% for the selected agent.

In patients with HAP/VAP with risk factors for MRSA infection (Table 1), patients in units where greater than 10% to 20% of *S. aureus* isolates are methicillin resistant, and patients in units where the prevalence of MRSA is unknown, empiric coverage should include agents targeting MRSA (vancomycin or linezolid). The guidelines don't provide a preference for use of vancomycin over linezolid. The decision between the two should be guided by patient-specific factors.

A weak recommendation is provided to avoid aminoglycosides and colistin for empiric therapy if other viable agents with adequate gram-negative activity are available to prevent side effects.

Importantly, the guidelines do not mention newer antimicrobial agents—ceftazidime-avibactam and ceftolozone-tazobactam, which are a welcome addition to the armamentarium available to treat MDR organisms. These new agents have been approved by the Food and Drug Administration for treatment of complicated intra-abdominal and complicated urinary tract infections, and skin and soft tissue infections. However, these agents must be used judiciously given their significant costs. Guidelines also underscore the importance of optimal antimicrobial dosing; dosing should be determined based on pharmacokinetic and pharmacodynamic data, rather than manufacturers' prescribing information.

DOUBLE COVERAGE FOR *PSEUDOMONAS*

Dual antipseudomonal agents from different classes are recommended for empiric therapy in the 2016 HAP/VAP guidelines in patients with a risk factor for MDR gram-negative pathogens (Table 1), patients in units where more than 10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and patients in an ICU where local antimicrobial susceptibility rates are not available. In addition, all patients who have bronchiectasis or cystic fibrosis, who have received intravenous (IV) antibiotics in the last 90 days, and who are at high risk for mortality, including the need for ventilator

support due to pneumonia or septic shock, should receive dual empiric antipseudomonal agents.[1] While the authors acknowledge that multiple studies have demonstrated no difference in clinical outcomes between monotherapy and double coverage for *Pseudomonas*, dual antipseudomonal empiric therapy is recommended in certain patients to increase the likelihood of at least one of the agents being active empirically.

A meta-analysis was performed to evaluate the role of combination therapy as empiric treatment for VAP. This analysis included 41 trials and 7,015 patients. Overall mortality was 20.3%, and treatment failure occurred in 37.4% of patients who could be evaluated microbiologically. No mortality differences were observed between any of the regimens compared. The combination of ceftazidime/aminoglycoside was found to be inferior to meropenem (two trials, relative risk [RR], 0.70; 95% confidence interval [CI], 0.53–0.93). Rates of mortality and treatment failure for monotherapy compared with combination therapy were similar (11 trials, RR for mortality with monotherapy, 0.94; 95% CI, 0.76–1.16; RR of treatment failure with monotherapy, 0.88; 95% CI, 0.72–1.07).[8]

To further investigate these results, a prospective, open-label, randomized study in ICU patients with VAP was performed to determine the efficacy and safety of empiric meropenem monotherapy (1 g IV daily) compared with the combination of ceftazidime (2 g IV every eight hours) plus amikacin (15 mg/kg IV daily). A total of 140 patients receiving mechanical ventilation and diagnosed with pneumonia were included in the study. Clinical responses of cure or improvement were achieved in 68.1% of meropenem-treated patients and 54.9% of ceftazidime/amikacin-treated patients (RR, 1.25; 95% CI, > 1.00–1.55). When nonevaluable patients were excluded from the analysis, the satisfactory clinical response was 82.5% and 66.1% for the meropenem and ceftazidime/amikacin patients, respectively ($P = 0.044$). Adverse events were found to be slightly higher in the combination group (11.3%) than in the monotherapy group (10.1%).[9]

Similar results were also seen in a prospective, multicenter study by Sieger et al. that was an unblinded, randomized trial to evaluate the efficacy and tolerability of IV empiric treatment with meropenem compared with ceftazidime-tobramycin in patients with HAP. Two hundred and eleven patients were enrolled; 121 were evaluable for the analysis of both clinical and bacteriological efficacy. Satisfactory clinical responses occurred in 89% of the meropenem-treated patients and in 72% of the ceftazidime-tobramycin-treated patients ($P = 0.04$), with corresponding bacteriological response rates of 89% and 67%, respectively ($P = 0.006$). The frequency and profile of drug-related adverse events were similar across treatment groups.[10]

Another randomized trial was done to compare a strategy of combination therapy with a strategy of monotherapy using broad-spectrum antibiotics for suspected late VAP. This study included 740 mechanically ventilated patients who developed suspected VAP. Patients who were known to be colonized or infected with *Pseudomonas* or MRSA or who were immunocompromised were excluded. Patients were allocated to receive meropenem and ciprofloxacin or meropenem alone. The results showed no difference in 28-day mortality between the combination and monotherapy groups (RR, 1.05; 95% CI, 0.78–1.42; $P = 0.74$) or in secondary endpoints, including duration of ICU and hospital stay or treatment response, between the two groups. However, in a subgroup of patients who had infection due to *Pseudomonas* species, *Acinetobacter* species, and MDR gram-negative bacilli at enrollment (n = 56), the *in vitro* susceptibility of the organism to initial antibiotics ($P < 0.001$) and microbiological eradication of infecting organisms ($P = 0.05$) was higher in the combination group compared with the monotherapy group, with no differences in clinical outcomes.[11]

Based on the studies cited above, decisions about dual coverage should be individualized, and there are situations where it may be reasonable: 1) empiric therapy for critically ill patients at risk of infection with MDR pathogens to increase coverage and likelihood of adequate initial therapy; and 2) empiric therapy in institutions with a high rate of resistance/MDR organisms.

DURATION OF THERAPY

In most patients with HAP/VAP, the recommended duration of antibiotic therapy is seven days, regardless of the isolated pathogen(s). This recommendation was based on two meta-analyses.[1]

In the first meta-analysis, four randomized controlled trials comparing short regimens (seven to eight days) with long regimens (10 to 15 days) were identified. No difference in mortality or relapse was found between the compared arms ($P = 0.32$ and $P = 0.06$, respectively), but there was an increase in antibiotic-free days in favor of the short-course treatment with a mean difference of 3.40 days ($P = 0.001$).[12]

The second meta-analysis by Pugh et al. included six studies involving 1,088 participants. For patients with VAP, overall a short seven- to eight-day course of antibiotics compared with a prolonged 10- to 15-day course increased 28-day antibiotic-free days and reduced recurrence of VAP due to MDR organisms, without affecting mortality and other recurrence outcomes. However, for cases of VAP caused by nonfermenting gram-negative bacilli, recurrence was greater after short-course therapy, though mortality was the same.[13]

Hedrick et al. conducted a retrospective, single-center study examining VAP caused by nonfermenting gram-negative bacilli to determine whether shorter courses of antibiotic therapy were associated with higher rates of recurrence. Of the 452 episodes of VAP, 154 were associated with nonfermenting gram-negative bacilli. Twenty-seven patients were treated with three to eight days of antibiotics, whereas 127 received more than 10 days of therapy. The recurrence rates for infection and mortality were similar between the two groups ($P = 0.27$ and $P = 0.38$, respectively).[14]

Recent data from Klompas et al. have demonstrated that very short antibiotic courses (one to three days) may be sufficient for certain patients. They conducted a retrospective study including 1,290 patients with suspected VAP but minimal and stable ventilator settings. The antibiotic course of one to three days was compared to courses of more than three days. Overall, there were similar outcomes of time to extubation alive (HR, 1.16 for short- versus long-course treatment; 95% CI, 0.98–1.36), ventilator death (HR, 0.82; 95% CI, 0.55–1.22), time to hospital discharge alive (HR, 1.07; 95% CI, 0.91–1.26), or hospital death (HR, 0.99; 95% CI, 0.75–1.31) between the two groups.[15]

Overall, the available data suggest there was no difference between short-course (seven to eight days) and long-course (10 to 15 days) antibiotic regimens in regard to mortality, treat-

ment failure, recurrent pneumonia, or duration of mechanical ventilation. This is a change from the old guidelines, which suggested that certain pathogens should be treated with longer durations due to risk of recurrence, which was not seen in recent studies.[1] It is important to note that regardless of the new recommendations, longer courses may still be appropriate in some circumstances where the patient may have a delayed clinical response.

The guidelines recommend that discontinuation of antibiotics in HAP/VAP patients be based on clinical criteria and procalcitonin (PCT) testing, a potentially helpful biomarker when patients are on longer-than-recommended antibiotic courses. PCT has been studied vastly as a tool to determine the need for continued antibiotic administration. Several recent analyses have demonstrated that the use of PCT decreased antibiotic usage without incurring treatment failure or increasing mortality. A meta-analysis of 14 trials (4,221 patients) investigated PCT use in acute respiratory infections; the results demonstrated a decrease in antibiotic exposure of 3.47 days (95% CI, 3.17–3.78).[16] However, it important to note that these trials had limitations, such as unblinding and control groups often on longer treatment courses. In addition to a quick turnaround time for this test, there must be physician buy-in to act upon the results. Furthermore, it is important to note that the benefits of PCT are unclear if patients are getting seven-day standard therapy.

SUMMARY

The 2016 HAP/VAP guidelines can be implemented with extensive education to all providers on what an antibiogram is, how to use a local antibiogram to choose empiric therapy, and how it impacts clinical outcomes. An important point to keep in mind is that not all patients with HAP/VAP should be given vancomycin. The addition of this drug is only indicated in the setting of risk factors. Empiric broad-spectrum antimicrobial use in a patient with presumed sepsis is imperative; however, the re-evaluation of clinical status and antibiotic administration with the use of procalcitonin testing could shorten the duration of therapy even further for patients without proven HAP/VAP. This leads to less antibiotic exposure and less risk of potential adverse events, such as colonization or infection with MDR organisms and *Clostridium difficile*.

Efforts should also be made to improve antibiotic utilization, optimal antimicrobial dosing, and duration of therapy. This reduction in duration of therapy from routine practice will decrease days of exposure to antibiotics, minimizing the risk of developing resistance.

KEY POINTS

- HCAP has been removed from the HAP/VAP guidelines. The main reason for this removal is that contact with the health care system is not a strong predictor of risk for MDR bacteria. HCAP risk factors were neither sensitive nor specific to identify at-risk patients.
- Get to know your microbiologist(s) and antibiograms; utilize your local antibiograms to select empiric therapy.
- HAP/VAP treatment should always include antipseudomonal coverage. Coverage of MRSA should be added if the patient has risk factors.
- Antimicrobial dosing should be determined using pharmacokinetic and pharmacodynamic data, rather than manufacturers' prescribing information.
- De-escalation should be practiced actively, especially in clinically responsive patients with negative cultures.
- Procalcitonin levels may be used in combination with clinical criteria to guide discontinuation of therapy in patients with HAP/VAP.
- Despite a seven-day duration of antibiotic therapy, certain clinical scenarios may warrant longer courses of therapy.
- There are insufficient data to recommend the routine use of combination therapy, but dual coverage may be warranted in select circumstances.

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